

### **REMARKS/ARGUMENTS**

Upon entry of this amendment, claims 42-52 are pending in this application and are presented for examination. Claims 1-41 have been canceled without prejudice. Claims 42-52 are newly added. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

#### **I. FORMALITIES**

Support for new claims 42-52 is found throughout the specification as filed. A detailed description of the support for new claim 42 is provided below. Support for new claims 43-44 is found, for example, on page 5, lines 23-26. Support for new claim 45 is found, for example, on page 3, lines 3-9. Support for new claim 46 is found, for example, on page 19, lines 3-5. Support for new claim 47 is found, for example, from page 41, line 30 to page 42, line 1. Support for new claim 48 is found, for example, on page 42, lines 2-9 and on page 45, lines 11-19. Support for new claim 49 is found, for example, on page 17, lines 15-24 and on page 45, lines 11-19 and 24-32. Support for new claim 50 is found, for example, on page 3, lines 19-25, on page 15, lines 30-32, and on page 45, lines 29-32. Support for new claim 51 is found, for example, on page 45, lines 29-32. Support for new claim 52 is found, for example, on page 45, lines 24-28. Thus, no new matter has been introduced. As such, Applicant respectfully requests that the new claims be entered.

#### **II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Claims 30-41 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter and lacking sufficient written description. In particular, the Examiner alleges that claims 30-41 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled the art that Applicant, at the time the application was filed, had possession of the claimed invention. In response, Applicant has canceled claims 30-41 without prejudice, thereby rendering this rejection moot. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Newly added claim 42 recites a method for diagnosing inflammatory bowel disease (IBD) in a subject comprising determining an expression level of at least one gene product in a sample from the subject, wherein the gene product is an mRNA of a gene selected from the group consisting of macrophage inflammatory protein-2 $\beta$  (GRO3), neutrophil lipocalin (HNL), elastase specific inhibitor (elafin), and type VI collagen  $\alpha$ 3 chain (COL6A3); and comparing the expression level of the gene product in the subject to an expression level of the gene product in a healthy subject, wherein a difference in the expression level of the gene product indicates that the subject has IBD or is at risk of developing IBD.

Applicant believes that newly added claim 42 finds clear support in the specification as filed. For example, the specification discloses that the methods of the present invention can be used to diagnose an inflammatory bowel disease (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) (*see*, page 41, lines 15-20). The specification also discloses that a level of expression of an IBD gene product is determined in a sample (*see*, page 3, lines 10-11). In particular, the sample is obtained from a subject and the expression level of the gene product (*i.e.*, the mRNA level) is determined and compared to the level of the gene product in a healthy subject (*see*, page 42, lines 6-8). A difference in the expression level of the gene product (*i.e.*, an abnormal mRNA level) indicates that the subject has IBD or is at risk of developing IBD (*see*, page 42, lines 8-9).

Table 1 describes a list of the genes identified by Applicant whose gene products display differential expression in UC or CD relative to control samples. In particular, Table 1 shows that the macrophage inflammatory protein-2 $\beta$  (GRO3) gene product is overexpressed by 3.4-fold in UC relative to control samples (*see*, page 51, class I). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (X53800) into the National Center for Biotechnology Information (NCBI) online database (<http://www.ncbi.nlm.nih.gov/>). For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Similarly, Table 1 shows that the neutrophil lipocalin (HNL) gene product is overexpressed by 35.5-fold in UC relative to control samples (*see*, page 51, class II). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its

GenBank accession number (S75256) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Likewise, Table 1 shows that the elastase specific inhibitor (elafin) gene product is overexpressed by 13.3-fold in UC and 3.8-fold in CD relative to control samples (*see*, page 55, class VII). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (L10343) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Finally, Table 1 shows that the type VI collagen  $\alpha 3$  chain (COL6A3) gene product is overexpressed by 7.3-fold in UC relative to control samples (*see*, page 56, class VII). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (X52022) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

In view of the foregoing, Applicant believes that new claim 42 is adequately disclosed in the specification as filed.

### **III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claims 30-41 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In response, Applicant has canceled claims 30-41 without prejudice, thereby rendering this rejection moot. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

### **IV. REJECTION UNDER 35 U.S.C. § 103(a)**

A. Claims 30-41 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Alexander *et al.* (*Digestive Diseases and Sciences*, 41:660-669 (1996)) in view of Poulakkainen *et al.* (*Gastroenterology*, 114:A1064 (1998)) and Prehn *et al.* (*Gastroenterology*, 114:A1064 (1998)) and further in view of the specification. Applicant has canceled claims 30-41 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

As discussed above, newly added claim 42 recites a method for diagnosing IBD in a subject comprising determining an expression level of at least one gene product in a sample from the subject, wherein the gene product is an mRNA of a gene selected from the group consisting of macrophage inflammatory protein-2 $\beta$  (GRO3), neutrophil lipocalin (HNL), elastase specific inhibitor (elafin), and type VI collagen  $\alpha$ 3 chain (COL6A3). The method further comprises comparing the expression level of the gene product in the subject to an expression level of the gene product in a healthy subject, wherein a difference in the expression level of the gene product indicates that the subject has IBD or is at risk of developing IBD.

However, Alexander *et al.* simply fails to teach or suggest that any of the claimed genes (*i.e.*, GRO3, HNL, elafin, or COL6A3) are differentially expressed in IBD relative to control samples. Rather, Alexander *et al.* discloses the differential expression of 8 protooncogenes (*i.e.*, H-ras, c-myc, c-fos, c-jun, junB, N-myc, c-abl, and c-yes) in colonic epithelial cells of IBD patients. Similarly, Prehn *et al.* does not teach or suggest that any of the specific genes set forth in new claim 42 are differentially expressed in IBD relative to control samples. In fact, Prehn *et al.* does not teach the differential of any genes; rather, this reference discloses that IL-18, IL-12, IL-10, and IL-4 protein levels as determined by an immunoassay (*i.e.*, ELISA) remained unchanged in cells that were treated with TNF- $\alpha$ . Likewise, Puolakkainen *et al.* fails to teach or suggest that any of the specifically claimed genes are differentially expressed in IBD relative to control samples. Rather, Puolakkainen *et al.* discloses the differential expression of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (MMP-12), and TIMP-3 in intestinal ulcerations. As a result, Applicant asserts that these three references, either alone or in combination, fail to teach or suggest the claimed invention.

In the Office Action, the Examiner alleges that the genes disclosed in Table 1 of the instant specification are not novel and are well known for their role in IBD (*see*, page 10 of the Office Action). In response, Applicant asserts that the Examiner has improperly characterized these genes as being well known for their role in IBD. With regard to new claim 42, Applicant submits that although the specifically claimed genes were known in the art, their role in IBD was never appreciated. In fact, the instant specification is the first to show that

GRO3, HNL, elafin, and COL6A3 are differentially expressed (*i.e.*, overexpressed) in UC and/or CD relative to control samples. As such, Applicant believes that new claim 42 would not be rendered obvious by the instant specification, alone or in combination with Alexander *et al.*, Prehn *et al.*, and/or Puolakkainen *et al.*

**B.** Claims 30-41 were also rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)) and Poulakkainen *et al.* Applicant has canceled claims 30-41 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Again, newly added claim 42 recites a method for diagnosing IBD in a subject comprising determining an expression level of at least one gene product in a sample from the subject, wherein the gene product is an mRNA of a gene selected from the group consisting of GRO3, HNL, elafin, and COL6A3. The method further comprises comparing the expression level of the gene product in the subject to an expression level of the gene product in a healthy subject, wherein a difference in the expression level of the gene product indicates that the subject has IBD or is at risk of developing IBD.

However, Dieckgraefe *et al.* does not teach or suggest that any of the specific genes set forth in new claim 42 are differentially expressed in IBD relative to control samples. Rather, Dieckgraefe *et al.* only provides a general disclosure of classes of genes that were differentially expressed in IBD specimens, without reference to any particular genes in those classes. Likewise, as discussed above, Puolakkainen *et al.* fails to teach or suggest that any of the specifically claimed genes are differentially expressed in IBD relative to control samples. As a result, Applicant asserts that these references, either alone or in combination, fail to teach or suggest the claimed invention.

**C.** Claims 30-41 were further rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* in view of the specification. Applicant has canceled claims 30-41 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Once again, newly added claim 42 recites a method for diagnosing IBD in a subject comprising determining an expression level of at least one gene product in a sample from

the subject, wherein the gene product is an mRNA of a gene selected from the group consisting of GRO3, HNL, elafin, and COL6A3. The method further comprises comparing the expression level of the gene product in the subject to an expression level of the gene product in a healthy subject, wherein a difference in the expression level of the gene product indicates that the subject has IBD or is at risk of developing IBD.

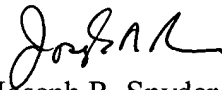
However, as described above, Dieckgraefe *et al.* does not teach or suggest that any of the specific genes set forth in new claim 42 are differentially expressed in IBD relative to control samples. Additionally, as discussed above, Applicant asserts that the Examiner has improperly characterized the genes disclosed in Table 1 of the instant specification as being well known for their role in IBD. Again, with regard to new claim 42, Applicant submits that although the specifically claimed genes were known in the art, their role in IBD was never appreciated. In fact, the instant specification is the first to show that GRO3, HNL, elafin, and COL6A3 are differentially expressed (*i.e.*, overexpressed) in UC and/or CD relative to control samples. As such, Applicant believes that new claim 42 would not be rendered obvious by the instant specification, alone or in combination with Dieckgraefe *et al.*

**V. CONCLUSION**

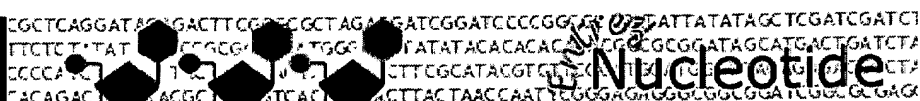
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

  
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Reg. No. 39,381

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Two Embarcadero Center, Eighth Floor  
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Tel: 925-472-5000  
Fax: 415-576-0300  
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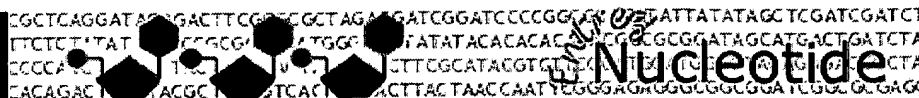
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## Links

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ORGANISM Homo sapiens

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REFERENCE 1 (bases 1 to 534)

AUTHORS Bartsch, S. and Tschesche, H.

**TITLE** Cloning and expression of human neutrophil lipocalin cDNA derived from bone marrow and ovarian cancer cells

JOURNAL FEBS Lett. 357 (3), 255-259 (1995)

PUBMED 7835423

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 REFERENCE 1 (bases 1 to 9930)  
 AUTHORS Chu,M.L., Zhang,R.Z., Pan,T.C., Stokes,D., Conway,D., Kuo,H.J.,  
 Glanville,R., Mayer,U., Mann,K., Deutzmann,R. and Timpl,R.  
 TITLE Mosaic structure of globular domains in the human type VI collagen  
 alpha 3 chain: similarity to von Willebrand factor, fibronectin,  
 actin, salivary proteins and aprotinin type protease inhibitors  
 JOURNAL EMBO J. 9 (2), 385-393 (1990)  
 PUBMED 1689238  
 REFERENCE 2  
 AUTHORS Chu,M.L.  
 TITLE Direct Submission  
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 of Biochemistry & Molec Biology, 233 South 10th Street,  
 Philadelphia, PA 19107, USA  
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10501 atttatacaa agaaactttt taataaagta tattgaaagt taaaaaaaa aaaaaaaa

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